Exhibit C
Shulman Affid.

Room M-009
Wellesley Hospital
Toronto, Ont.
Sept. 30, 1983

Mrs. B.D. Thorn
Director of Finance and Administration
The Arthritis Society
920 Yonge St., Suite 420
Toronto, Ont. M4W 3J7

Dear Mrs. Thorn,

Enclosed is a report summarizing my recent and current research activities.

I would like again to take this opportunity to express my gratitude to the Arthritis Society for its support in these endeavors

Yours sincerely,

Marc J Shulman

Dr. Marc J. Shulman

Annual Report to the Arthritis Society

September, 1983

Dr. Marc J. Shulman

Molecular Requirements of Immunoglobulin Gene and Protein Function

Our work this last year concentrated in large part on the development of tools for analysing the structural basis of protein and gene function. We have developed methods of introducing DNA carrying the immunoglobulin μ and κ genes into immunocompetent cells where it directs the synthesis of functional IgM(κ). Our success with this technique has opened many avenues of research, and we shall concentrate on but a few where we are particularly well organized.

One project which we began last year is designed to test whether chimeric (partly mouse - partly human) antibodies should be considered as potentially useful agents for therapy. Immunoglobulin has a bipartite structure - the variable (V) region determines antigen binding specificity; the constant (C) region mediates functions such as complement activation and Fc receptor binding. Specific monoclonal antibodies might have a role in the therapy of human disease: tumor specific antibodies might be effective in promoting tumor regression; in autoimmune diseases, it might be possible to use specific antibodies to manipulate the deleterious immune response of the patient. Human immunoglobulin might work

better than mouse immunoglobulin for such purposes. However, the antigen binding specificities obtainable for human immunoglobulin might be too limited because of the ethical restrictions on human immunization. A possible solution combining the best of the mouse and human systems might be to make chimeric immunoglobulin genes in which a V region from a mouse immunoglobulin is joined to the human C region. We have begun to test whether the chimeric gene encoding such immunoglobulin can in fact function and whether the antigen binding specificity of the chimeric immunoglobulin is the same as for the original mouse immunoglobulin. To date we have verified that the chimeric μ heavy chain gene is expressed well, and immunoglobulin bearing the chimeric μ chain combined with the mouse light chain retains the antigen binding capacity. Currently we are testing the function of the chimeric κ gene.

Another area of our research is to define the molecular requirement for complement (C') activation by IgM, i.e. to identify the amino acids on IgM which are important for C' activation. This long standing problem in immunochemistry is now solvable because we can alter the IgM encoding DNA in vitro, generating mutant sequences so that the effects of amino acid replacements can be assessed. Here we are fortunate in having previously isolated naturally occurring mutant mouse cell lines, producing IgM which is defective in C' activation. Our work at the present time involves the isolation and nucleotide sequence analysis of these natural mutations. The results of this analysis will probably indicate which regions of the

immunoglobulin genes should be mutagenized in vitro. Using the chimeric immunoglobulin system described above, we will be able to analyse human as well as mouse IgM in this way.

In a quite different project, we have continued our work which identified murine DNA transpons - sequences in mouse DNA which under some as yet undefined conditions are copied and inserted elsewhere in the mouse genome. We have shown that these sequences are homologous to the RNA found in the retrovirus-like intracisternal type A particle. We have continued to characterize the effects of these insertions on the expression of nearby genes. We expect to undertake an extensive study of the mechanism and requirements for transposition.

Abstracts of papers presented at the meeting on

CELLULAR AND MOLECULAR BIOLOGY OF NEOPLASIA

October 2nd — October 6th 1983

Organizing Committee:

A. Bernstein, R.N. Buick, T.W. Mak, R.A. Phillips and I. Tannock

Symposium Coordinator:

Susan Oliphant

Ontario Cancer Institute, Toronto, Ontario, Canada